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A simple method of calculation for tumor therapies plus an observation on the log-kill hypothesis. Short communication

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Abstract

We describe a simple method of calculating therapies associated to any required tumor outcome, for models obeying the so-called log-kill hypothesis. When this method is applied to some particular cases of the Gompertz model, we find some contradictions with the desired goal of obtaining tumor cure under therapy. The contradictions do not depend on the particular calculative method used.

Key words: tumor growth, therapy, mathematical model, log-kill hypothesis, inverse problem.

Un método simple para calcular terapias en tumores, mas una observación sobre la hipótesis de muerte logarítmica. Comunicación corta

Resumen

Se describe un método sencillo para calcular terapias asociadas a cualquier resultado requerido de evolución de un tumor, para modelos que obedecen la hipótesis de muerte logarítmica. Cuando se aplica esta técnica a algunos casos particulares del modelo de Gompertz, se encuentra contradicciones con el resultado deseado de obtener curación como resultado de la terapia. Las contradicciones no dependen del método particular usado en los cálculos.

Palabras clave: crecimiento tumoral, terapia, modelo matemático, hipótesis de muerte logarítmica, problema inverso.

1. Introduction

Mathematical modeling allows better understanding of complex dynamics (1), help in principle to establish the decisive factors in the struggle of therapies and tumor (2), permit to elucidate the possible implications of typical features in cancer from a theoretical standpoint (3) and identify future directions for experimental research (4).

Tumor growth models assume that tumors, $x(t)$ in the absence of interactions grow at a rate described by a function $G(x)$, and we mention that there is no agreement

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on the functional form of the law ruling tumor growth because it seems that each tumor type follows its own pattern. Some authors claim to have arrived to a universal law for tumor growth (5, 6), but that statement has aroused some polemic (7). In what follows we limit to mention some well-known models: a) logistic, $G(x) = x(1 - x / B)$, where x is the tumor's density and B is the carrying capacity of the system; b) gompertzian model (8), $G(x) = -Ax\log(x / x_\infty)$, where x is the number of tumor cells, A^{-1} is related to the doubling time and x_∞ is the tumor asymptotical limit; c) potential (9), $G(x) = \alpha x^\beta$, where x denotes the tumor mass, α is the tumor growth coefficient and β is a positive parameter indicator for the tumor's growth rate. Good fitting to experimental data is achieved with $\beta = 0.42$; d) dynamical universal (6), $G(x) = ax^p\left[1 - \left(\frac{x}{X}\right)^{1-p}\right]$, where x is the mass of the tumor, a is a parameter related to the particular tumor metabolic rate, X, is the tumor asymptotical limit, and p, is a variable parameter satisfying $2 / 3 < p < 1$.

The models for tumor-therapy interaction assume that a therapy (Chemotherapy or Radiotherapy), $C(t)$, causes a tumor number's of cells rate decrement. The simplest model assumes that a fixed number of cells is killed by a certain dose of therapy regardless of the number of tumor cells present (fixed number kill hypothesis), this gives $\frac{dx}{dt} = -k_1 C(t)$. The log-kill hypothesis or fractional-kill hypothesis assumes that tumors are destroyed by therapies at a rate proportional to the product of their respective values, therefore $\frac{dx(t)}{dt} = -k_2 x(t)C(t)$. A more complex alternative is to assume that the growth inhibiting effect of a treatment is proportional to the growth rate of the untreated tumor times its size (10), then $\frac{dx}{dt} = -k_3 xG(x)C(t)$. We here limit to mention the fractioned therapy model, rooted in log-kill hypothesis, the linear-quadratic model (11), the models based in evolutionary game theory (12) and the *in silica* models (13). Some models assume that antitumor response to therapy depends both upon total dose, dose per fraction, and inversely upon the overall time during which radiotherapy is administered (14). There are many other models for tumor-therapy interaction, but our goal in this letter is not to make a revision of that important issue, the interested reader can find additional discussion in the reference (15). It seems unnecessary to say that every aspect of tumor evolution can be modeled. Just as an illustration, we cite the models on tumor-immune system interaction (1, 2), with therapy added (16, 17). Difficulties appear when working these models because they are described by systems of coupled differential equations lacking of a closed solution, so the researcher must rely on qualitative analysis and numerical integration for working them.

2. Mathematical results

2.1. Generalities

The full equation for a tumor, $x(t)$ with growth rate $G(x)$, under the effect of a therapy $C(t)$, under the log-kill hypothesis is:

$$\dot{x}(t) = G(x) - kx(t)C(t). \qquad [1]$$

It is straightforward to prove that equation [1] has a solution, if we assume that (a) $G(x)$ is continuous everywhere, and (b) $C(t)$ is bounded in any finite interval. (For the Gompertzian model it is necessary to use also the equality:

$$x_2 \log x_2 - x_1 \log x_1 =$$

$$\int_{x_1}^{x_2} \log \tau \, d\tau = (x_2 - x_1)\log \xi,$$

where $\xi \in [x_1, x_2]$). Given a couple $G(x)$ and $C(t)$, the modeler currently introduces approximations for $x(t)$ in order to find a closed solution for equation (1). Very common mis-

takes when working with small values of x are taking $G(x) \approx x$ in the previous models b), c) and d); or considering $C(t)$ a driving term as it is currently done in elementary forced harmonic oscillator because both oversimplifications lead to untrue results. In what follows we specialize in the Gompertzian model.

2.2. The Gompertz model

This model comes from actuarial sciences, and it was originally used for describing populations in which growth is inhibited by its own increasing size and they tend to an asymptotical limit. The model is described by the following equations (8):

$$\frac{dx}{dt} = k_1 x(t) g(t); \frac{dg}{dt} = -Ag(t). \qquad [2]$$

With solution:

$$x(t) = x_0 \exp\left[K(1 - e^{-At})\right], \qquad [3]$$

where $K = \log\left(\frac{x_\infty}{x_0}\right)$, x_0 is the initial tumor number of cells and x_∞ its asymptotical limit. The previous model can be written as (see the reference (8)):

$$\frac{dx}{dt} = -Ax\log\left(\frac{x}{x_\infty}\right). \qquad [4]$$

The equivalent forms of the Gompertz equation have different uses. The system [2] is complicated and it is traditionally avoided (8). The equation [3] is currently used for parameters determination, whilst the equation [4] for its simplicity is preferred by modelers. As Gompertz equation is expressed in different forms, each one using diverse time scales, care must be paid to the numerical values obtained in each instance because Gompertzian parameters result to be sensitive to the detailed form of the equation used for obtaining them. Values for x_0, x_∞ and A can be found in (8, 18, 19, 20). In references (8, 18) time is days, (19) uses months and (20) uses years. We shall use the values given in (19), $x_0 = 10^9$, $x_\infty = 3.1 \times 10^{12}$, $\log A = -2.9$.

2.3. Traditional approach

For the Gompertzian model as given in the equation [4], under the log kill hypothesis, we obtain as full equation:

$$\frac{dx}{dt} = -Ax\log(x / x_\infty) - kxC(t), \qquad [5]$$

the well known change $x = e^y$ in equation [5] gives:

$$x(t) = x_\infty \exp\left[e^{-At}\left(\log\frac{x_0}{x_\infty} - k\int_0^t e^{As}C(s)ds\right)\right] \qquad [6]$$

and $x(t)$ immediately follows for any given $C(s)$. Then the problem of determining the tumor's final value, given a therapy to be administered during a time t_S, is straightforward. The therapist can, at least in principle, determine the outcome of an applied treatment at the cost of evaluating the integral appearing in the equation [6]. The interested reader can find a list of therapies, $C(s)$, and their respective theoretical tumor responses, $x(t)$, some of them qualitatively analyzed in the reference (21).

2.4. Alternative approach

Now we propose an inverse approach: for a ***desired*** tumor decay law *x(t)*, ***this decay based in clinical or physiological patient's characteristics***, what therapy should be applied? (This is a departure from the current policy of expecting nothing but a cure from a treatment; additionally we are imposing the way of tumor evolution. If we introduce the Gompertzian growth in our Eq. [1], we obtain:

$$C(s) = \frac{1}{k}\left[(\dot{x} / x) + A\log(x / x_\infty)\right]. \qquad [7]$$

Then it is a simple matter calculating the therapy $C(s)$ that will produce the tumor eradication on the desired schedule. We say that there exists a space of tumors, $x(t)$, and a space of therapies, $C(s)$, both related by our equations [6] and [7]. This is similar to the elementary use of Fourier transform for defining a space of functions and its related space of transforms. It is worth to remark that the therapy to be applied should be compatible with tolerance or toxicity thresholds for the healthy cells, and a test on the important point of compatibility is mandatory. This issue is not dealt with in this work; the interested reader should consult the reference (22).

3. Discussion

In what follows we shall consider some simple examples of application of the equations [6] and [7]. We begin with $C(s) = C_0$, a constant. Then the application of the equation [6] gives

$$x(t) = x_0 \exp\left[e^{-At}\left(\log\frac{x_\infty}{x_0}\right) - \frac{C_0 k}{A}\left(1 - \exp[-At]\right)\right],$$

and the tumor evolves to the asymptotical non null-value:

$$x(t) = x_\infty \exp(-C_0 k / A). \qquad [8]$$

(Fractioned therapies are based on reiterative application of this result). Note that $x(t) > 0$ after a therapy spanning very long time ($t_S \to \infty$). As, for instance, tumors and caquexia are intimately related (23), the equation [8] implies the permanence in the patient's body of a harmful metabolites source. The following example is $C(s) = s$, then

$$x(t) = x_\infty \exp\left[\frac{A}{k^2} - \frac{A}{k}t\right]\exp\left[e^{-At}\left(\log\frac{x_0}{x_\infty} + \frac{A}{k^2}\right)\right],$$

with asymptotical limit:

$$x(t) = x_\infty \exp\left[\frac{k}{A^2} - \frac{k}{A}t_S\right], \qquad [9]$$

a time decreasing function as desired by the physician, but a question is posed on the implementation of such therapy because $C(s)$ is a monotonous growing time function, and it becomes arbitrarily high for time arbitrarily long. The reader should not forget the meaning of the limit $t_S \to \infty$ (very long treatment time) when considering asymptotical expressions.

We now give an example for the use of our equation [7]: we try a lineal decay under a therapy lasting t_S, *under the log-kill hypothesis*, and the questions are: Which therapy yields this output? It is such therapy attainable? We take a linearly decrementing tumor:

$$x(t) = -\left(\frac{x_0 - x_1}{t_S}\right)t + x_0, \qquad [10]$$

where $x_0 = x(t = 0)$ is tumor number of cells when commencing therapy, x_1 is one cell, $-\dfrac{x_0 - x_1}{t_S}$ is the desired tumor decrease rate $\dot{x}(t)$, and t_S is the whole time of therapy's application. Introducing the expressions for $x(t)$ and $\dot{x}(t)$, in the equation [7], we obtain the exact result,

$$C(s) = -\frac{1}{k}\left[\frac{x_1 - x_0}{x_1 s + x_0(t_S - s)} + A\log\left(\frac{(x_1 - x_0)s}{x_\infty t_S} + \frac{x_0}{x_\infty}\right)\right],$$

[11]

a logarithmically growing therapy. Note that:

$$C_0 = C(t = 0) \cong -\frac{1}{k}\left[\frac{-x_0}{x_0 t_S} + A\log\left(\frac{x_0}{x_\infty}\right)\right], \qquad [12]$$

and:

$$C(t_S) \cong -\frac{1}{k}\left[-\frac{x_0}{x_1 t_S} + A\log\left(\frac{x_1}{x_\infty}\right)\right]. \qquad [13]$$

We use now the well-known values of the Gompertzian parameters for computing $A\log(x_1 / x_\infty) \approx -1.52$, $A\log(x_0 / x_\infty) \approx -0.38$, then the logarithmic term is negligible in the equation [13]. If we take $1 \le t_S \le 100$ (months), we arrive to:

$$\frac{C(t_S)}{C_0} \cong \frac{x_0}{x_1(1+0{,}38 t_S)} \ge 2.5\times 10^7. \qquad [14]$$

Therefore the required therapy's intensity $C(t_S)$ at the end of treatment becomes technically infinite. We find that for obtaining the desired achievement of no tumor, we will require a) an everlasting therapy, or b) a therapy of monotonously growing intensity and therefore unrealizable by the techniques available nowadays.

Many examples of Gompertzian growth linked to log-kill hypothesis seem to be just hand waving. The following example was taken from the reference (21). Consider the therapy given by:

$$C(s) = -\frac{1}{k}\left[A\log\frac{x_\infty(1+\beta s^\gamma)}{x_0} + \frac{\gamma\beta s^{\gamma-1}}{1+\beta s^\gamma}\right], \qquad [15]$$

where β and γ are positive but otherwise unknown parameters. Introducing the equation [15] in the equation [6] we obtain the exact solution:

$$x(t) = \frac{x_0}{1+\beta t^\gamma}. \qquad [16]$$

(Alternatively the reader can introduce the equation [16] in the equation [7] for obtaining the therapy, $C(s)$). The couple defined by the equations [15] and [16] is twofold attractive: First, the therapy is *very slowly* growing; second the tumor asymptotically decreases. When introducing the numerical values $x_0 \cong 10^9$, $x(t_S) = 1$, we obtain $t_S \cong \left(\frac{x_0}{\beta}\right)^{1/\gamma}$ and the ratio final therapy/initial therapy turns out to be $\frac{C(t_S)}{C_0} \cong 4.18 + 2.63\frac{\gamma}{t_S}$. As elegant as can be the equations [15] and [16] and the relations derived from them, they don't allow neither computing the relevant time t_S of therapy application nor to arrive to any conclusions on the therapy's intensity, because neither the β and γ parameters were provided nor a method for their experimental determination was proposed. Note, finally, that couples of equations as [15] and [16], or [10] and [11] do not depend on the way of arriving at them.

4. Conclusions

We present a simple technique to calculate therapies obeying the log-kill hypothesis; this technique, which implies differentiation procedures, seems to be simpler than the traditional one using integration. The resulting expressions are independent from the way they have come about, so here we discuss the calculations simplicity. We also obtain that tumor eradication both from theoretical and numerical examples is an unachievable goal, at least for models that have been analyzed here, if the tumour-therapy interaction is ruled by a log-kill law. As it is well known that adjuvant therapy cures some patients is early stage breast and colon cancer, our results suggest that log-kill hypothesis is incorrect al least for these cancers. The curious fact is that already in 1977 (10, 24), some authors, using fitting of experimental data, suggested a model not ruled by the log-kill law for the tumor-therapy interaction. Thirty years have gone by and this alternative became widely known as the Norton-Simon hypothesis. We cite (25) a paper issued in 2005: Therapy results in a rate of regression in tumor volume that is proportional to the rate of growth that would be expected for an unperturbed tumor of that size. As therapies

based on the log-kill hypothesis (among them radiotherapies) are routinely applied over millions of patients, it seems necessary to make a revision of the transcendental subject of finding the law ruling the tumour-therapy interaction.

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